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Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population☆

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ABSTRACT

Cadmium (Cd) was a developmental toxicant that induces fetal malformation and growth restriction in mice. However, epidemiological studies about the association of maternal serum Cd level with risk of preterm birth were limited. This study was to investigate whether maternal serum Cd level during pregnancy is associated with risk of preterm birth in a Chinese population. Total 3254 eligible mother-and-singleton-offspring pairs were recruited. Maternal serum Cd level was measured by GFAAS. Based on tertiles, maternal serum Cd concentration was classified as low (L–Cd, <0.65 μg/L), medium (M–Cd, 0.65–0.94 μg/L) and high (H–Cd, ≥0.95 μg/L). Odds ratio (*OR*) for preterm birth was estimated using multiple logistic regression models. Results showed the rate of preterm birth among L–Cd, M-Cd and H–Cd was 3.5%, 3.8%, and 9.4%, respectively. Subjects with H–Cd had a significantly higher risk for preterm birth (*OR*: 2.86; 95%*CI*: 1.95, 4.19; $P < 0.001$) than did those with L–Cd. Adjusted *OR* for preterm birth was 3.02 (95%*CI*: 2.02, 4.50; $P < 0.001$) among subjects with H–Cd compared to subjects with L–Cd. Taken together, the above results suggest that maternal serum Cd level during pregnancy is positively associated with risk of preterm birth.

1. Introduction

Cadmium (Cd) is a ubiquitous occupational and environmental toxicant. Workers in electroplating, pigments, paints, welding, and Ni–Cd batteries are usually exposed to a high concentration of Cd (Beveridge et al., 2010). Environmental Cd pollution has pervaded many parts of the world, especially the developing countries such as China and India. According to First National Soil Pollution Survey (2005–2013) from 31 provinces in China, the geoaccumulation index values for Cd in 17.5% soil samples lay above the moderately contaminated level (Chen et al., 2015). A 19-year follow-up study demonstrated that a significant increase in Cd concentrations of urine and an obviously worsened renal dysfunction were observed in Cd-polluted areas of China (Zhang et al., 2014). In addition, a recent study also found that Cd in natural soils was taken up substantially by crops in southwestern China (Liu et al., 2015). As Cd pollution in soil and cigarette smoke is ubiquitous, the general population is exposed to a low concentration of Cd via food and cigarette smoking (Honda et al., 2010).

There is a growing body of evidence suggesting that Cd is a reproductive toxicant in humans. Several epidemiological investigations show that environmental exposure to a low concentration of Cd is associated with male infertility and poor semen quality in humans (Pant et al., 2003; Telisman et al., 2000; Wu et al., 2008; Xu et al., 1993, 2003). Cd is a testicular toxicant in rodent animals (Siu et al., 2009). Numerous experimental studies indicate that Cd induces germ cell apoptosis in mouse testes (Ji et al., 2011b, 2012a, 2012b, 2013; Kim and Soh, 2009; Ozawa et al., 2002). At a high dose, Cd is also embryotoxic and teratogenic in rodents (Thompson and Bannigan, 2008). Our previous study showed that

Abbreviations: BMI, body mass index; C-ABCS, China-Anhui Birth Cohort Study; Cd, cadmium; *CI*, confidence intervals; FAAS, flame atomic absorption spectrophotometry; GA, gestational age; GFAAS, graphite furnace atomic absorption spectrometry; LBW, low birth weight; LMP, last menstrual period; *OR*, odds ratios; ROS, reactive oxygen species; Zn, zinc.

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Cd accumulated mainly in maternal liver and kidney, and only trace amounts of Cd could pass from dam to placentas and fetuses (Wang et al., 2016). A large number of experimental studies demonstrate that maternal Cd exposure at middle gestational stage causes fetal malformations (Hovland et al., 1999; Paniagua-Castro et al., 2007; Robinson et al., 2009; Scott et al., 2005; Veeriah et al., 2015; Wang et al., 2012). Several reports indicate that maternal Cd exposure at late gestational stage induces fetal growth restriction in rodents (Ahokas et al., 1980; Ji et al., 2011a; Selvaratnam et al., 2013).

Preterm birth, defined as spontaneous or iatrogenic delivery before gestational week 37 (Englund-Ogge et al., 2014). Numerous epidemiologic data demonstrate that there is an association between preterm birth and childhood asthma (Goyal et al., 2011; Romero et al., 2014). Moreover, preterm birth increases the risk of cardiovascular diseases in young adulthood and is also an important independent risk factor for neurodevelopmental disorders (Crump et al., 2010; Sonnenschein-van der Voort et al., 2014; Ueda et al., 2014). Although some potential risk factors, such as temperature, maternal smoking, maternal zinc deficiency during pregnancy, maternal obesity and inflammation, have been identified, the exact etiology for preterm birth remain obscure (Cnattingius et al., 2013; Savitz et al., 2014; Scharfe-Nugent et al., 2012; Scholl et al., 1993; Strand et al., 2012). Nevertheless, whether maternal Cd exposure during pregnancy induces preterm birth in humans needs to be further determined.

The present study was to analyze the association between maternal serum Cd level during pregnancy and risk of preterm birth in a large population-based birth cohort study. We found that maternal Cd exposure significantly elevated risk of preterm birth. Recently, Our results showed that maternal Cd exposure during pregnancy disrupted zinc (Zn) metabolism in mice (Wang et al., 2016). Thus, the present study also analyzed the association between maternal serum Cd and Zn level.

2. Material and methods

2.1. Study population

China-Anhui Birth Cohort Study (C-ABCS) is a prospective population-based cohort study that recruited 16, 766 pregnant women from six major cities of Anhui province in China between November 2008 and October 2010. A total of 13, 454 singleton live births were followed up from this cohort (Tao et al., 2013). The present study analyzed a sub-study of the C-ABCS cohort that recruited 4, 358 pregnant women from Hefei city of Anhui province from January 1 to December 31 in 2009 (Tao et al., 2013). Exclusion criteria for participation were as follows: inability to provide informed consent, alcohol drinking and cigarette smoking during pregnancy, mental disorders, pregnancy-induced hypertension and preeclampsia, gestational diabetes, heart disease, thyroid-related disease, a history of ≥3 previous miscarriages, or plans to leave the locale before delivery (Tao et al., 2013). For this study, eligible participants were mother-and-singleton-offspring pairs in which serum samples from mothers were available for subsequent Cd measurements and offspring had detailed birth records. Total 36 twins, 15 fetal deaths, 2 stillbirths, 58 abortions and 589 withdrew were excluded from the current study (Fig. 1). In addition, 306 with no maternal sera available and 98 with samples collected in the third trimester were also excluded (Fig. 1). As a result of differences in time at entry into Hefei cohort, 1122 serum samples were collected in the first trimester (4–12 weeks of gestation), and 2132 serum samples were collected in the second trimester (13–27 weeks of gestation). As above, the inclusion rate of the current study was 74.7 percent (3254/4358). The present study was approved by the ethics committee of Anhui Medical University (permit 08-1026). The methods were carried out in accordance with the approved guidelines.

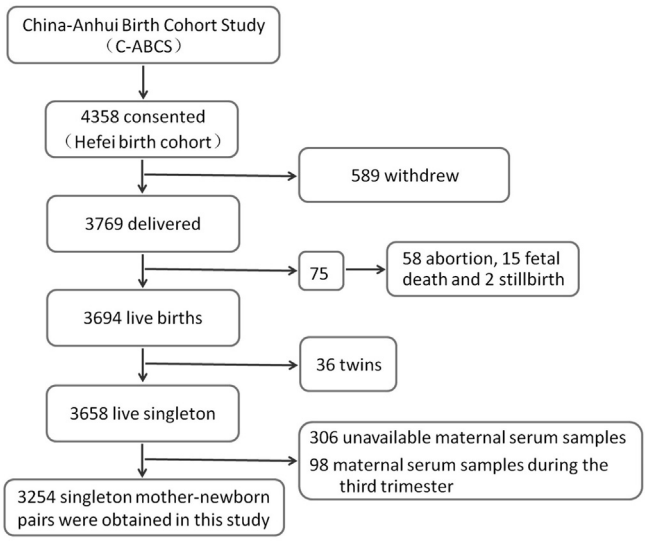

Fig. 1. Flow diagram of recruitment and follow-up in this birth cohort study.

2.2. Outcomes

Gestational age (GA) was calculated using mother's last menstrual period (LMP). In the present study, preterm birth was defined as births at <37 gestational weeks (Athalye-Jape et al., 2014). Total 181 premature infants with spontaneous and non-medical preterm birth were then identified. In addition, preterm birth can be further sub-divided into early preterm birth (<32 weeks), moderate preterm birth (32 to <34 weeks) and late preterm birth (34 to <37 weeks) according to a recently described method (Katz et al., 2013). The present study further analyzed the association between maternal serum Cd level and risks for different sub-categories of preterm birth (early, moderate or late preterm birth).

2.3. Measurement of serum Cd concentration

To avoid contamination of exogenous Cd, all polypropylene tubes and pipette tips were soaked for at least 24 h in 10% ultrapure HNO_3 at room temperature and rinsed persistently in deionized water before use. Maternal fasting blood during pregnancy was collected in the morning. After discarding hemolytic specimens, available sera were stored at −80 °C until analysis. Serum Cd concentration was determined by graphite furnace atomic absorption spectrometry (GFAAS; model: TAS-990; Purkinje General Instrument Co., Ltd, Beijing, China) coupled with a deuterium-lamp background correction system. All samples were prepared and analyzed according to a slightly modified method as previously described(Ji et al., 2011a). Serum samples were diluted with 1% HNO_3 according to 1:4 (v/v). Matrix modifiers colloid palladium (Colpd™, Xinda Measuring & Control Technology Co., Ltd, Chengdu, China) were added to each standard, blank and sample dilution. The following diluted solution was then detected using GFAAS. Each sample was analyzed in triplicate. Precision of the method was measured by coefficients of variation. Mean CV for measurement of serum Cd was 5.16% for within-day determinations and 6.55% for day-to-day determinations. The limit of detection was 0.01 μg/L. In addition, the accuracy of the GFAAS method was also evaluated by the recovery rate of the standard addition method for cadmium. The average recovery rate using standard addition method is